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A REVIEW OF INFORMATION ON ANABASINE AND NORNICOTINE, 1938-1944

(Supplement to E-537 and E-561)

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CONTENTS

|                                                                                 | Page |
|---------------------------------------------------------------------------------|------|
| Introduction . . . . .                                                          | 2    |
| Chemistry of anabasine . . . . .                                                | 2    |
| Occurrence of anabasine and nornicotine . . . . .                               | 3    |
| <u>Anabasis</u> . . . . .                                                       | 3    |
| <u>Duboisia</u> . . . . .                                                       | 3    |
| <u>Nicotiana</u> . . . . .                                                      | 3    |
| Occurrence of nornicotine in commercial nicotine sulfate . . . . .              | 6    |
| Extraction of anabasine from plants . . . . .                                   | 6    |
| Composition of commercial anabasine sulfate made from <u>Anabasis</u> . . . . . | 7    |
| Analytical methods . . . . .                                                    | 7    |
| Separation of anabasine from nicotine and other alkaloids . . . . .             | 8    |
| Pharmacology of anabasine and nornicotine . . . . .                             | 11   |
| Anabasine . . . . .                                                             | 11   |
| Nornicotine . . . . .                                                           | 11   |
| Insecticidal value of anabasine . . . . .                                       | 12   |
| Thysanoptera . . . . .                                                          | 12   |
| Homoptera . . . . .                                                             | 13   |
| Hemiptera . . . . .                                                             | 14   |
| Diptera . . . . .                                                               | 14   |
| Coleoptera . . . . .                                                            | 15   |
| Anoplura . . . . .                                                              | 15   |
| Patents . . . . .                                                               | 15   |
| Literature cited . . . . .                                                      | 16   |

MAR 21 1945

## INTRODUCTION

In April 1941 the Bureau of Entomology and Plant Quarantine issued E-537, A Review of Information on Anabasine, and in March 1942 E-561, A Review of Information on Nornicotine. These reviewed 163 and 50 publications, respectively. The purpose of the present publication is to bring up to date all available information on both these promising insecticides.

In preparing this review the following abstract journals, published from 1938 to 1943, inclusive, were searched: Biological Abstracts, Chemical Abstracts, Chemisches Zentralblatt, Experiment Station Record, Index Medicus, and Review of Applied Entomology (Series A and B). In addition the Quarterly Bibliography on Insecticide Materials of Vegetable Origin through No. 26 (January to March 1944), issued by the [Great Britain] Imperial Institute Consultative Committee on Insecticide Materials of Vegetable Origin, was consulted.

## CHEMISTRY OF ANABASINE

The following constants for anabasine are given: Boiling point (p = 238 mm.) 280.9° C., freezing point 9°, specific rotation -83.1°. Its parachor coincides closely with the theoretical parachor.-- Sokolov (75).

In a report on the reactions of amino-N-methylanabasines the following melting points are given:

|                                | <u>° C.</u> |
|--------------------------------|-------------|
| alpha-Amino-N-methylanabasine  | 95 - 95.3   |
| Derivatives:                   |             |
| Acetyl -----                   | 72 - 73     |
| Diacetyl, hydrate -----        | 60.5- 62.5  |
| alpha'-Amino-N-methylanabasine | 91.5- 92.3  |
| Derivatives:                   |             |
| Acetyl -----                   | 122 - 122.5 |
| Propionyl -----                | 97 - 98     |
| Benzoyl -----                  | 104 - 106   |
| Dibenzoyl -----                | 142 - 143   |

The picrate of the alpha compound decomposes at 238-239.5°, and that of the alpha' compound at 227.5-228°. The boiling point of the diacetyl derivative is 160-162° (p = 4 mm.), and that of propionyl derivative (p = 5.5 mm.) 193-200°.--Kabachnik and Zitser (32).

The dihydrochloride of dichloroanabasine is obtained by passing chlorine into anabasine in cold alcohol. The yield is 29-63 percent. It melts at 203.7° C. (dec.) Free dichloroanabasine dissolves in water with difficulty, is soluble in ethyl alcohol, slightly less soluble in ether, and melts at 51-3°. It reacts with picric acid, forming a picrate,

melting at 91-5°. Nicotinic acid is formed by oxidizing dichloroanabasine with a permanganate solution. Bromination of anabasine under the same conditions forms bromo-substituted compounds, melting at 105° and 135°, which are very hygroscopic and very unstable. At 80-100° they are decomposed by water with the separation of anabasine. The amount of bromine decreases considerably on prolonged keeping of the bromo-substituted compounds. The picrate of one bromo-substituted compound melts at 199-201°, and according to its bromine content it corresponds to a monobromoanabasine.-- Dashkevich (20).

#### OCCURRENCE OF ANABASINE AND NORNICOTINE

The most important sources of anabasine are the tree tobacco, Nicotiana glauca, a native of Argentina and Uruguay, and the Russian shrub, Anabasis aphylla, which is related to the American tumbleweed. Although N. glauca is a native of South America, it is very much at home in Mexico and in the southwestern United States.-- Higbee (27).

A review of information on anabasine discusses sources, chemistry, alkaloids of Anabasis aphylla, physiological action, insecticidal properties, and commercial forms used for pest control.-- Holman (28, pp. 21-25).

A comprehensive review on the alkaloids of tobacco includes nornicotine and anabasine.-- Jackson (31).

#### Anabasis

The anabasine content of Anabasis aphylla was found to be inversely proportional to the degree of moisture. However, this relationship cannot be accepted as an absolute rule without further verifications.-- Kudryavtsev (34).

Anabasis aphylla contains anabasine, lupinine, aphyllidine, and aphylline. The preparation of salts and other derivatives is described. Anabasine, upon reacting with boiling 5-percent hydrochloric acid, undergoes ring opening.-- Spath, Galinovsky, and Mayer (82).

In a study of saline plants of Turkmania Anabasis aphylla was found to contain 2 percent (dry basis) of potassium nitrate.-- Sabinin, Baslavskaya, Beloussova, and Schocklender (60).

#### Duboisia

Analyses of samples of Duboisia hopwoodii received from Australia showed nornicotine to be the only alkaloid present, as follows: Leaves 3.31, leaves on twigs 1.92, twigs without leaves 0.95, and larger stems 0.52 percent.-- Bowen (10).

#### Nicotiana

From the steam-volatile fraction of extracts of cured tobacco leaves, volatile bases other than nicotine amounting to at least 6.5 percent of the total alkaloid content were obtained. The dipicrate of a base isolated from this nornicotine fraction decomposed at 179.5-180.5° C. (uncor.). This base reacted with nitrous acid and with benzoyl chloride in the manner described by Pictet and Rotschy (ref. 30 in E-561) for nicotimine.-- Vickery and Pucher (85).

The volatile and nonvolatile alkaloid contents of the following species of Nicotiana are given: acuminata, alata, chinensis, glauca, glutinosa, langs-

dorffii, longiflora, paniculata, plumbaginifolia, quadrivalvis, repanda, rusbyi, rustica, sanderæ, suaveolens, sylvestris, tabacum. The alkaloid content of a number of hybrids is given.-- Shmuk and Khmura (68).

Nicotiana tabacum normally contains nicotine but no anabasine, whereas N. glauca contains only anabasine. When N. glauca was grafted on N. tabacum, formation of the characteristic alkaloid proceeded in stock and scion with a considerable increase in the anabasine content of the scion over that of the control plant. Anabasine appeared to be formed in the stock also. When N. tabacum was grafted on N. glauca, nicotine was completely replaced by anabasine in the scion while a trace of nicotine appeared in the stock.-- Shmuk, Kostov, and Borozdina (69).

When Nicotiana rustica was grafted to N. glauca, it lost nicotine and accumulated anabasine.-- Shmuk (63).

The grafting of nicotine-containing tobacco on the nicotine-free species, Nicotiana glauca, resulted in plants in which the nicotine was completely replaced by anabasine.-- Evtushenko (22).

A study was made of the inheritance of nicotine and anabasine content by Nicotiana tabacum x Nicotiana glauca hybrids, and interaction of stock and scion when these species are grafted. In hybrids a change was noted in the type of alkaloids with reference to position of the leaves.-- Kuz'menko and Tikhvinskaya (35).

Nornicotine was identified in the following species of Nicotiana: benthamiana, ingulba, longiflora, palmeri, sanguinea, solanifolia, suaveolens, sylvestris, and trigonophylla.-- Shmuk (64).

A large number of representative Nicotiana species and hybrids were examined for alkaloids. All 29 of the wild species contained 1 or more alkaloids. N. alata, bigelovii, gossei, and wigandioides apparently contained only nicotine. N. glutinosa, maritima, otophora, tomentosa, and trigonophylla apparently contained only nornicotine. N. debneyi and glauca contained largely d,l-anabasine. In debneyi about 15 percent of the total alkaloid was nicotine, whereas in glauca a much lower percentage of this alkaloid was found. The remaining 18 species contained mixtures of nicotine and nornicotine. Nicotine was predominant only in N. benavidesii, langsдорffi, and stocktoni; in longiflora and plumbaginifolia it was not possible to determine which of the two alkaloids was present in the higher concentration; and in the rest nornicotine predominated. No wild species studied had as much as 2 percent total alkaloid content, and most species had less than 0.5 percent. In 23 species 84 to 100 percent of the total alkaloid content was taken up by the main alkaloid. In crosses between N. tabacum, which contains mostly nicotine, and species whose alkaloid complex was made up largely or entirely of nornicotine, the hybrids contained mainly nornicotine, together with small amounts of nicotine. The F<sub>1</sub> and amphidiploid N. tabacum (nicotine) x N. glauca (anabasine) contained mostly anabasine with some nicotine. In one sample of this F<sub>1</sub> a trace of nornicotine was detected.-- H. H. Smith and C. R. Smith (74).

A method is presented for classifying tobacco broadly into three types according to their picrate melting points-- (1) the

nicotine type, 215-224 °C.; (2) the mixed type, 190-215°, indicative of both alkaloids as major components; and (3) the nornicotine type, 175-200°. Of 90 samples of tobacco examined, 2 were of the nornicotine type. One, Robinson's Maryland Medium Broadleaf, was investigated by Markwood (refs. 25 and 26 in E-561); the other, Flue-cured Cash, may prove equally valuable as a source material of nornicotine. Two tobaccos were of the mixed type; the others were of the nicotine type.-- Markwood and Barthel (46).

The 42 species of Nicotiana, when analyzed by an improved procedure which is described, can be divided into 4 groups as follows: (1) The main alkaloid is nicotine, secondary pyridine alkaloids being absent or present only in insignificant quantities; (2) the main alkaloid is nornicotine, tertiary pyridine alkaloids being absent or present only in insignificant quantities; (3) a mixture of nicotine and nornicotine, and (4) the main alkaloid is anabasine.-- Shmuk and Borozdina (67).

A simplified method is presented for the identification of alkaloids of tobacco. The essence of the method is the formation of the picrates of the secondary base and submission of it to methylation without isolation of the pure amine; for effectiveness it is sufficient to have 2 to 10 mg. of the alkaloid. The picrate of the base is methylated quantitatively by heating with formaldehyde and formic acid. The presence of nornicotine by this procedure was shown in various members of the tobacco family. Determination of the picrate melting point both before and after methylation enabled the nornicotine to be identified in the presence of nicotine. Anabasine and piperidine are also methylated by this procedure.-- Shmuk (64).

In order to find a more logical basis for a classification of tobaccos, the melting points of picrates prepared from known mixtures of nicotine and nornicotine were determined. The steam-volatile alkaloids were separated from the plant material by distillation and the melting point of the mixed picrates of the alkaloids was compared with that of the known-mixture picrates. In the curve prepared from the known-mixture-picrate melting points and composition the slope of the right-hand side was sufficient to warrant establishment of a division at composition two-thirds nicotine and one-third nornicotine, and temperature 211°C. Hence, tobaccos, the alkaloids of which give a picrate with the upper limit of the melting range above this point, are considered as the "nicotine type." The division point at composition one-third nicotine and two-thirds nornicotine, and temperature 196°C., falls in a region of marked discontinuity of melting-point behavior and is therefore even more suitable to set off the "nornicotine type" of tobacco. This leaves the interval 196° to 211°C. as characteristic of "mixed type" of tobacco. Tobaccos were analyzed for nicotine and nornicotine, and the analysis and the melting point of the picrate of the steam-volatile alkaloids from the sample were compared with the composition-melting point curve. The close agreement of the relative percentage compositions and melting points obtained from the tobacco samples with those of known solutions has been used with considerable success in estimating the relative composition of these alkaloids in samples.--Bowen and Barthel (15).

Nornicotine may be identified in tobacco, insecticidal tobacco preparations, and nicotine preparations by comparing the melting point of the mixed picrates of the steam-volatile alkaloids with the picrate melting point of a methylated sample thereof. Methylation of the nornicotine gives nicotine; consequently, the picrate of the methylated alkaloids will melt at the same point as nicotine picrate and no depression of melting will occur in a mixed-melting-point determination with nicotine picrate in those cases where steam-volatile alkaloids other than nicotine and nornicotine are substantially absent.--Bowen and Barthel (16).

When nightshade (Solanum nigrum), Datura stramonium, and tomato plants, usually free of nicotine, were grafted separately on tobacco (Nicotiana tabacum and N. rustica), they were enabled to form this alkaloid and store it in the leaves and fruit. Large quantities of nicotine will form in the scions, if the leaves are removed from the tobacco stock at the time of intensive growth of the scions and the root of tobacco is present. When tobacco is used as the scion in graft upon the same plants, nicotine disappears entirely from the graft system and cannot be detected in the stock or scion. When N. glauca, which contains anabasine, was grafted on a tomato plant, as much anabasine was formed by the scion as occurred in the control plant of N. glauca raised under normal conditions.--Shmuk, Smirnov, and Il'in (70).

#### OCCURRENCE OF NORNICOTINE IN COMMERCIAL NICOTINE SULFATE

Two commercial samples of nicotine sulfate were found to contain nornicotine, in one amounting to nearly 12 percent of the alkaloid content. This finding is important because nornicotine has been reported to be more toxic than nicotine to aphids. Commercial nicotine preparations containing nornicotine may be expected to be better contact insecticides than those of pure nicotine. Since nornicotine is known to be less volatile than nicotine, when a mixture of the two is used as a fumigant, the predominant effect is believed to be that of nicotine. The presence of nornicotine in materials considered to be pure nicotine products could easily account for erratic and nonreproducible entomological results.-- Bowen and Barthel (12).

#### EXTRACTION OF ANABASINE FROM PLANTS

Steam distillation under pressure can be used to remove anabasine from plant material.-- Sokolov (78).

Of the water-immiscible solvents for the extraction of anabasine, ethylene dichloride is the best for yield and for velocity of extraction. Anabasine combines rapidly with the impurities in technical ethylene dichloride only during the initial stage of standing, after which anabasine is not decomposed and is only partially transferred to the residue with the slowly separating products of the reaction. The optimum ratio of solvent to raw material is 2:1. A semi-production-scale apparatus and experiments are described.-- Sokolov and Trupp (81).

The diffusion process of producing anabasine by the water-kerosene method is described. Proteins, which are especially harmful in the further treatment of the alkaloids, are decreased sharply by the presence of sodium chloride. The maximum yield of the alkaloids was 98 percent. In the countercurrent-diffusion process the average period of extraction depends on the temperature of the water; it could be reduced to 20 to 30 minutes.-- Sokolov and Demonterik (79).

A report on the production of anabasine sulfate from Anabasis aphylla at Tchinkent, U.S.S.R., has been published.-- Iljin (30).

#### COMPOSITION OF COMMERCIAL ANABASINE SULFATE MADE FROM ANABASIS

Commercial anabasine sulfate solution is reported to contain 21.52 percent of anabasine, 7.52 percent of lupine, 10.45 percent of aphyllidine and aphylline, 12.19 percent of total sulfates, 1.68 percent of free sulfuric acid, and 1.24 percent of inorganic impurities.-- Dashkevich (19).

An improved method for the isolation of lupinine from commercial anabasine sulfate solution was devised. The crude alkaloid mixture was separated by the Orekhov method (ref. 98 in E-537) and distilled in vacuo. The low-boiling fraction 136-9° (p = 12 mm.) consists of lupinine and anabasine. The mixture is dissolved in dry toluene and treated with metallic sodium with stirring and heating. On cooling the sodium lupinate is filtered off, washed with dry toluene, and treated with water, the mixture is extracted with petroleum ether, and the extract dried and concentrated to yield crystalline lupinine (97 percent recovery). The mother liquor after distillation yields anabasine. The use of petroleum ether for washing sodium lupinate also appears to give a better product than toluene. The best results were obtained when petroleum ether was used as the medium for the reaction with metallic sodium.-- Sadykov and Lazur'evskii (61).

In 1935 it was reported that Russia produced 2,500 tons of insecticides (powders, soaps, and solutions) containing anabasine or anabasine sulfate.-- Bocharova (8).

#### ANALYTICAL METHODS

A method for the microchemical detection of anabasine in legal chemical investigations has been described. When Dragendorff's reagent is added to solutions of anabasine, characteristic crystals are obtained which may be used for the microchemical detection of the alkaloid in material from the cadaver. In this way as little as 1 microgram of anabasine in a drop of solution can be detected. The anabasine is extracted from the organs by repeated digestion of the ground material with alcohol to which tartaric acid has been added in amounts sufficient to give an acid reaction to litmus. The extract is concentrated in vacuum, the protein removed, the alcohol evaporated, and the material subjected to preliminary purification with chloroform. The tartrate is then converted into the base by treatment with ammonia, and the base is extracted with chloroform. After removal of the chloroform the anabasine can be tested for directly, or after further purification of the solution.-- Shvaikova (71).

A rapid method is proposed for determining total alkaloids in semimanufactured products and waste materials in the production of anabasine. The alkaline extract is extracted with ethylene dichloride and the ethylene dichloride extract titrated with hydrochloric acid (litmus indicator). For determination in Anabasis the raw material is extracted with water, a part of the water extract is made alkaline, and the analysis conducted as above.-- Sokolov (76).

#### Separation of anabasine from nicotine and other alkaloids

A titration method for determining the total alkaloid content of a mixture is proposed which is based on the fact that the acetyl derivative of anabasine does not form a picrate and nicotine does.-- Khmura (33).

Anabasine can be separated from the alkaloids associated with it in Anabasis aphylla by precipitation as fluosilicate from a solution in ethyl or methyl alcohol. The fluosilicate,  $C_{10}H_{14}N_2H_2SiF_6 \cdot H_2O$ , m.p.  $239^\circ(\text{dec.})$ , can be converted to the free base by reaction with sodium hydroxide. Anabasine is precipitated with alcoholic fluosilicic acid from an alcoholic medium. The precipitate is dissolved in hot water and titrated with a 0.1 N sodium hydroxide solution (thymolphthalein indicator). Nicotine can be determined similarly. Nicotine can be distinguished from anabasine by the solubility of its fluosilicate in methyl alcohol; fluosilicates of both are insoluble in ethyl alcohol.-- Sokolov (75, 77).

A comparative study was made of the reactions of anabasine, nicotine, and coniine. The Meltzer reagent (carbon disulfide, ethyl alcohol, and dilute copper sulfate solution) causes a white turbidity with nicotine and a black-brown turbidity with anabasine and coniine. All three alkaloids form characteristic crystals in saturated aqueous solution of picric acid. An ether solution of anabasine or nicotine, when mixed with an ether solution of iodine, first becomes turbid and then crystallizes. Coniine does not undergo this reaction. Mecke reagent (selenic acid and concentrated sulfuric acid) colors the anabasine residue pink, but does not change the color of nicotine or coniine with hydrochloric acid (sp. gr. 1.19). The coniine residue forms beautiful violet crystals after evaporation. No such crystals are formed from anabasine or nicotine. With nitric acid (sp. gr. 1.4) the nicotine residue assumes on slow heating a pink color, which changes to green. Under the same conditions no coloration of anabasine and coniine is observed. A maximum yield up to 95 percent of anabasine alkaloids is obtained by extraction of cadaver material with acidified alcohol.-- Razvadovskii (55).

The following directions for determining nicotine in the presence of anabasine are given: Treat the aqueous solution of the alkaloids with 3 ml. of 10-percent sulfuric acid and 10 ml. of freshly prepared 5-percent sodium nitrite, heat for 30 minutes at  $40-50^\circ$ , neutralize approximately by introducing 10-percent sodium hydroxide and then accurately by titration with 0.1 N sulfuric acid (with methyl orange), and add 3 to 4 drops of excess acid. Precipitate the picrates by addition of picric acid (12 gm. per liter) and cool for 4 hours. Filter, wash twice with 0.1-percent picric acid and twice with water, transfer to a glass-stoppered flask, add 15 to 20

ml. of water, and titrate with a 0.1 N alkali (phenolphthalein indicator), adding 5 ml. of toluene toward the end of titration. The amount of 0.1 N sodium hydroxide used multiplied by 0.0081 gives the content of nicotine. The method is based on the fact that nitrous acid, without affecting the nicotine, transforms the anabasine into the nitroso compound, which is not precipitated by picric acid under the above conditions.-- Shmuk and Borozdina (65).

Nicotine and anabasine, treated with an aqueous solution of aniline and a 5-percent solution of ammonium thiocyanate or potassium thiocyanate in bromine water, give a yellow color, which remains constant after the addition of 0.5 to 3.0 cc. of 5 to 10 percent sodium carbonate for nicotine, and changes to a bright rose for anabasine. The colored solutions can be compared in the colorimeter with corresponding standard solutions. However, the determination of anabasine and nicotine by the colorimetric method in plants was complicated by the other compounds containing the pyridine ring.-- Shmuk and Borozdina (66).

To identify the alkaloids of tobacco the picrates of nornicotine and anabasine can be methylated quantitatively by heating with formaldehyde-formic acid. Picric acid does not methylate under the conditions used. Determination of the melting point of the picrate before and after methylation enabled nornicotine to be identified in the presence of nicotine.-- Shmuk (64).

Nicotine forms an azeotropic mixture with water in a concentration of 2.5 gm. per 100 ml. This property is used in separating it from nornicotine or anabasine, or both. The separation of nicotine from a mixture of the three alkaloids was 97 to 103 percent of theory when the procedure consisted in distilling the mixed alkaloids from 125 ml. of water solution through the Widmer column to a low volume (about 15 ml.), adding 60 ml. of water containing 2 gm. of sodium chloride, and continuing again to a volume of 15 ml. The combined distillate was titrated and calculated as nicotine, but represents all the nicotine with some of the accompanying alkaloid or alkaloids. The titrated distillate was made alkaline with a slight excess of standard alkali to neutralize the standard acid, and the distillations were repeated as before but without the addition of sodium chloride. The combined distillate was titrated and the nicotine calculated.-- C. R. Smith (73).

The determination of nicotine and nornicotine in the presence of each other in aqueous solution is described. One portion of the solution is treated with sodium nitrite and acetic acid. The nitroso-nornicotine formed is not volatile in steam from a solution buffered at pH 10. The unchanged nicotine is steam-distilled off, and determined by acidimetric titration or by precipitation with silicotungstic acid. To another portion formaldehyde and formic acid are added to methylate the nornicotine to nicotine. The total alkaloid, now nicotine, is distilled off after addition of excess sodium hydroxide and determined as before. The difference between the two values represents the nornicotine. Details were developed for attaining an accuracy of 97 to 98 percent.-- Markwood (45).

An improved apparatus for the steam distillation of nicotine, nornicotine, and anabasine has been designed. This apparatus permits a longer contact between the steam vapor and the solution containing the alkaloids, which results in more rapid distillation than is possible by the conventional (A.O.A.C.) method.-- Bowen and Barthel (11).

A method is proposed for analysis of nicotine and nornicotine. Sodium chloride and strong sodium hydroxide greatly aid the distillation of nornicotine. The steam distillate containing both alkaloids is concentrated, and an aliquant treated with nitrous acid to form nitrosornicotine, which is not volatile with steam under the conditions at which the nicotine may be distilled (alkaline to phenolphthalein). Precipitation of the silicotungstates of the distillate containing the nicotine and of another aliquant containing both alkaloids furnishes the means of calculating the percentages of these alkaloids. The results of analyses of several samples of tobacco, *N. rustica*, and commercial nicotine sulfate solutions indicate an unexpectedly widespread occurrence of nornicotine. From a comparison of analyses made according to the A. O. A. C. method, it is evident that when nornicotine is present the accepted method of analysis for nicotine cannot be depended upon to give reliable results.-- Bowen and Barthel (13).

A test for the completeness of extraction of alkaloids from plant material is described which employs a slight modification of the method employed by Markwood and Barthel (see 46) for the liberation of the alkaloid from plant material. Approximately 5 gm. of the ~~material~~ is treated with 10 ml. of strong sulfuric acid (9 + 1), whereby the cellular structure is broken down with the formation of the sulfates of any remaining organic bases. After mixing for several minutes, water is added and the undissolved portion removed by filtration. The filtrate is neutralized with sodium hydroxide just acidified with hydrochloric acid and tested with silicotungstic acid solution. The test solution and reagent are warmed and then cooled with strong agitation. No precipitate indicates less than 0.01 percent of nicotine, nornicotine, or anabasine -- Bowen and Barthel (14).

A method of determining nicotine and nornicotine in mixtures of the alkaloids without preliminary separation is described. The method depends on the reactions of these compounds with cyanogen bromide to give, with nicotine, a pale yellowish-green color, and with nornicotine a red color. A 0.5- to 2-gm. sample of tobacco is steam-distilled from a solution containing salt and sodium hydroxide. This treatment insures a quantitative recovery of nornicotine, which is much less volatile with steam than is nicotine. A volume of the distillate containing not more than 80 micrograms of nicotine or 150 micrograms of nornicotine is treated with potassium dihydrogen phosphate, and then with freshly prepared cyanogen bromide reagent. After the color has been allowed to develop, the solution is transferred to a spectrophotometer and the intensity of the color developed by nornicotine is read at 540 millimicrons and that by nicotine at 375 millimicrons. Concentrations of the alkaloids are determined by inspection of previously prepared calibration curves. Since the color developed by nornicotine has an additive effect on the intensity of the color given by nicotine, the true concentration of

nicotine is equal to its apparent concentration minus the concentration of nornicotine. Factors influencing the development of the colors are discussed.-- Larson and Haag (37).

## PHARMACOLOGY OF ANABASINE AND NORNICOTINE

### Anabasine

Farmers in the Union of South Africa believed Nicotiana glauca to be deadly to ostriches, and it had been reported to be poisonous to cattle and sheep. In tests on rabbits the flowers were found to be slightly less toxic than the leaves. Rabbits died within 1.5 hours after being fed 30 gm. of the fresh flowers and within half an hour of eating the same dosage of fresh leaves. A sheep receiving 300 gm. of the fresh leaves through a stomach tube died within 2.5 hours.-- Steyn (84).

Anabasine solutions are fatal to animals when injected under the skin. Solutions of the equivalent compound anabasine-proto acid (obtained from soybeans and pea seeds) under the same conditions caused only slight poisoning. The rule of Traube stating the relation between the surface tension of a solution and its poisonous properties cannot be applied to solutions of anabasine-proto acid, since in spite of low surface tension such solutions do not kill experimental animals. Leont'ev and Smirnova (39).

Alpha-aminoanabasine possesses the fundamental pharmacological properties of anabasine but is less active. Its depressing action on the sympathetic ganglion of white mice is 1/75, its stimulating action on the cerebral layer and the kidney 1/75, its stimulating action on respiration 1/20 to 1/100, and its toxic action 1/16. The primary phase of the depression of respiration is absent; action on the blood pressure of decerebrate cats is less, and production of convulsions in white mice is greater, than with anabasine.-- Poluektov (54).

The introduction of acetyl, propionyl, and benzoyl groups in alpha- and alpha'-amino-N-methylanabasine decreases their respiratory stimulation but does not lower their toxicity.-- Kabachnik and Zitser (32).

The intravenous injection into rabbits of 2.5 to 6 mg. of anabasine sulfate per kilogram of body weight followed by repeated injections of 0.5 to 1.5 mg. per kilogram caused a decrease in the velocity of blood circulation in the lesser circulation system. The decrease was due to the action of anabasine sulfate in contraction of the blood vessels and the increased emission of adrenaline.-- Pleshchitsker (52).

### Nornicotine

On mice and dogs the toxic and vasopressor effects of smoke from a tobacco containing 0.13 percent of nicotine and 0.27 percent of nornicotine were due to the nicotine present, and relatively independent of the nornicotine content of the tobacco. On man the smoke from these low-nicotine cigarettes produced much less pronounced effects on blood pressure and pulse rate than did smoke from ordinary cigarettes.-- Haag and Larson (26).

A comparison has been made of the toxicity, the blood-pressure effects, and the fate in animals of levo-nornicotine, levo-nicotine, monomethylnicotinium iodide, isomonomethylnicotinium iodide, and dimethylnicotinium iodide. The integrity of the pyridine nitrogen appears to be essential to the high toxicity of nicotine and its methylated and demethylated derivatives. Progressive methylation of the pyrrolidine nitrogen increases the toxicity, as determined by intraperitoneal injection in mice, in the ratio 1:2:4 for nornicotine, nicotine, and monomethylnicotinium iodide. Difference in the dissociation constants of the three bases may be the explanation. In dogs the pressor effects of nornicotine and monomethylnicotinium iodide are, respectively, one-twelfth and two-thirds those of a molecular equivalent of nicotine. Isomonomethylnicotinium iodide and dimethylnicotinium iodide have practically no pressor action. The metabolism, in dogs, of the methylated and demethylated derivatives appears to be different from that of nicotine. No evidence was found that detoxication of nicotine in the animal body involves either methylation or demethylation.-- Larson and Haag (36).

#### INSECTICIDAL VALUE OF ANABASINE

Nicotiana tabacum, N. rustica, and N. glauca are mentioned as poisons for combating animal and plant pests.-- Sprenger (83).

Dipyridyls tested as contact insecticides were toxic to six species of aphids (bean, spinach, pea, turnip, apple, and rosy apple), adults and larvae of the Colorado potato beetle, and larvae of the three-lined potato beetle, the Mediterranean flour moth, and the silkworm. A crude dipyridyl oil [now known to have contained some neonicotine or anabasine] was more toxic than nicotine to certain insects.-- Richardson and Smith (58).

The alkaloids of Sophora are intermediate between anabasine and lupine in insecticidal power.-- Sokolov and Koblova (80).

The results of tests with anabasine on several species belonging to the orders Thysanoptera, Homoptera, Hemiptera, Diptera, Coleoptera, and Anoplura have been reported in the last six years.

##### Thysanoptera

Control measures for Heliothrips haemorrhoidalis (Bouché) in Russia included thorough spraying of the infested plants two or three times at intervals of 10 days with 0.5-percent nicotine sulfate or anabasine sulfate in 1-percent soap solution.-- Voitenko (86).

In Russia spraying with 7 to 10 gm. of anabasine sulfate and 40 gm. of soap in 40 liters of water was effective against adult thrips on mature flax.-- Shmeleva (62).

A marked reduction in infestation by Thrips lini Lad. (linarius Uzel) and a considerable increase in yield of flax can be obtained with a spray containing 0.3 or 0.2 percent of anabasine sulfate in 0.4-percent soap solution, or with a dust containing 5 percent of anabasine sulfate.-- Ermoloev (21).

Free anabasine at 1:1000 and 1:2000 and anabasine sulfate (40 percent anabasine) at 1:600 and 1:800, with and without sugar, showed high toxicity to the citrus thrips in laboratory experiments at Whittier, California. Sugar or some other added material is probably of value in retarding the loss of the toxic material. The thrips do not seem to feed on the anabasine-sugar residues. The material appears to act by contact and by fumigation. Although citrus thrips do not need to come in contact with the anabasine residue to be killed, the indicated range of the fumigation effect is less than a half-inch. The thrips underwent convulsions, followed by paralysis, within 9 to 14 minutes after their exposure to anabasine.-- McGregor (40, 42).

In orchard tests in the San Fernando Valley (Calif.) anabasine sulfate (1:600) with blood albumin gave marked reductions in the strain of citrus thrips resistant to tartar emetic. In similar tests at Whittier anabasine sulfate with sugar and with blood albumin gave high mortalities of the nonresistant strain. No injury to tender lemon leaves was detected from liquid applications of anabasine or anabasine sulfate.-- McGregor (41).

Tartar emetic was formerly the perfect control for citrus thrips, but a resistant race of thrips has developed. The best alternative at present is nicotine and sugar, which is satisfactory on lemons. The sulfate is superior to the alkaloid. Some work has been done with anabasine, but there is no clear-cut evidence that it is better than nicotine.-- Boyce (17).

Anabasine sulfate is recommended for use against thrips attacking flax and hemp in Russia.-- Nikiforov (48).

### Homoptera

The toxicity of anabasine was about equal to that of nicotine against aphids.-- Freak (23).

An infusion and a decoction of the leaves of Nicotiana glauca with soap (1 pound of leaves to 50 gallons of water) had a very slight effect on nasturtium aphids, while the powdered leaves had no apparent effect on them. The nicotine content of the leaves, determined upon a moisture-free basis, was only 0.18 percent.-- McIndoo and Sievers (43) [This plant contains anabasine, not nicotine.-- R. C. R.]

Anabasine sulfate mixed with beeswax and a fatty oil was one of the materials tested at Wenatchee, Wash., in experiments to prevent Eriosoma lanigerum (Hausm.) from infesting wounds in apple trees. No injury to plant tissues resulted from the application, but the effect on the aphids is not recorded.-- Reeves, Yothers, and Murray (57).

A spray containing anabasine sulfate (40 percent anabasine) at 1 to 1,000 in the first half of the season on lucerne [alfalfa], acacia, and cotton infested with (Doralis) Aphis laburni Kalt. and other cotton aphids gave excellent results in the Caucasus.-- Rekach (56).

A combination of solbar (barium polysulfide) and anabasine sulfate can be used for the simultaneous destruction of cucumber mildew and aphids. [These materials will react to form barium sulfate, free anabasine, and free sulfur.-- R. C. R.] A solution containing 0.5 percent of green soap and 0.3 percent of anabasine sulfate killed all the aphids.-- Zubov and Vasilevskii (87).

### Hemiptera

Concentration-mortality curves are given for solutions of various nitrogenous bases and soap when applied to the eggs of Lygaeus kalmii Stal, and the data are analyzed statistically. The following median lethal concentrations were obtained: Nicotine 0.11, quinoline 0.12, anabasine 0.18, piperidine 0.29, pyridine 19.6, and sodium oleate 2.0 percent. Quinoline was the only compound that killed the eggs at once. The others permitted development of the embryos to continue for several days. In some cases the young bugs were able to emerge from the eggs but died soon after hatching.-- C. F. Smith (72).

### Diptera

Of the stomach larvioides tested on Lucilia cuprina Wied. in Australia, anabasine sulfate (40 percent anabasine) was toxic at 0.1 percent concentration, whereas nicotine sulfate was toxic at 0.01 percent.-- Lennox (38).

In tests by P. M. Petrov of sprays against (Mayetiola) Phytophaga destructor (Say), preparations of anabasine gave the best results and were effective against the eggs.-- Ostapetz (49).

The effects of aerosols of anabasine sulfate and anabasine on Anopheles mosquitoes were investigated. The mosquitoes were very sensitive to anabasine solutions. The minimum lethal dose was 0.2 gm. of anabasine per cubic meter. The aerosol possesses an unpleasant odor, producing coughing, but under summer conditions it is dispersed rapidly and no odor remains after 15-20 minutes. To accelerate the reaction at low temperatures the mixture must be heated or some dry lime and sulfuric acid added. Anabasine may be volatilized by adding the free base or the sulfate to sand heated to 300-350°. The aerosol had no harmful effect on rabbits and hens, on the germinating properties of seeds, or on food products.-- Pogodina and Sokolov (53).

The toxicity of anabasine to mosquito larvae was much inferior to that of nicotine.-- Freak (23).

The toxicity indices of anabasine sulfate (35 percent anabasine) to Drosophila ampelophila Loew were determined in three kinds of baits as follows: In apple sirup 14.0, in molasses 7.2, and in cane sugar and glycerin 30.7. Sodium arsenite in the respective baits gives the following indices: 78.6, 62.8, and 63.7.-- Patterson (50).

In tests against the summer cabbage fly in Russia, the percentages of eggs destroyed by three applications of mercuric chloride (1:1000) were 95.3, of anabasine sulfate plus green soap 78.3, and of nicotine sulfate plus soap 76.0. The percentages of first instars destroyed by these three solutions were, respectively, 6.61, 2.6, and 3.6. They had no effect on the second and third instars.-- Galakhov (24).

When housefly eggs were dipped in an aqueous solution containing 3 percent by weight of anabasine, the mortality was within the same range (0 to 30 percent) as that caused by a solution containing 5 percent by weight of nicotine.-- Richardson (59).

### Coleoptera

Rhynchites bacchus L., (Coenorrhinus) R. pauxillus Germ., and Anthonomus pomorum (L.) are important pests of fruit trees in Russia. Dusting with calcium arsenate containing 7.5 percent of anabasine sulfate, or with a proprietary arsenical (Meritol), at rates of 13.5 and 27 pounds per acre, respectively, proved effective against all three species on apple.-- Ibatulina (29).

### Anoplura

A solution containing 2 percent of anabasine sulfate and 0.5 percent of green soap was completely effective against head lice, and had no harmful effect on the scalp.-- Pivovarov (51).

## PATENTS

Anabasine tannate is made by reacting 17.5 pounds of anabasine and 115 pounds of Chinese gallnuts in the presence of water. The product is insoluble in water and contains about 12 percent of the alkaloid. This patent covers the tannates of methylanabasine and of the mixture of alkaloids obtained from Anabasis aphylla.-- Arnold (1).

Anabasine bentonite is made in the same way that nicotine bentonite is made. Wyoming bentonite is treated with an excess of anabasine sulfate solution. After drying, the product contains about 14 percent of the alkaloid, of which one-half is water-soluble. Nornicotine bentonite may be made in the same manner.-- Arnold (2,4,5,6).

Anabasine and nornicotine may be substituted for nicotine in a dusting powder made by volatilizing the alkaloid, mixing it with exhaust gases, and bringing the mixture into contact with a dust suspended in gas. Suitable fumigating and dusting apparatus for treating a tree under a tent are described.-- Arnold (3).

An insecticidal dust is made by adding from 8 to 20 percent of free anabasine or nornicotine to an alkalized tobacco dust as a carrier and mixing 30 pounds of this with 70 pounds of clay.-- Arnold (7).

Anabasine can be dissolved in Freon-12 and applied as an

aerosol.-- Goodhue and Sullivan (25).

Nicotine, anabasine, and nornicotine are among the insecticides mentioned that can be used in combination with 2,3-dithiocyno-2,4,4-trimethylpentane for pest control, especially as a fly spray.-- Bousquet (9).

Derivatives of benzotetronic acid, including benzotetronic acid-alpha-carboxylic acid anabaside (made by combining the free acid and anabasine), are suitable insecticides for mothproofing wool.-- Martin (47).

Fatty acids from tung, linseed, fish, soybean, and other drying oils react with nicotine to form water-insoluble, nonvolatile, sticky fluids suitable for insecticide use.-- McKinney (44). [Although no mention is made of anabasine or nornicotine, they could be similarly used.-- R. C. Roark]

An insecticidal powder is made by mixing anabasine with a highly dispersible acid clay of limited adsorbing capacity.-- Dashkevich (18).

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